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Sesquiterpene composition of *Cinnamosma fragrans*: A Malagasy endemic plant used in traditional medicine



Composition en sesquiterpènes de Cinnamosma fragrans, une plante malgache endémique utilisée en médecine traditionnelle

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ABSTRACT

Cinnamosma fragrans is an endemic plant used in traditional medicine. The geographical distribution of this Canellaceae is limited to Madagascar. Few phytochemical investigations performed on this plant have described atypical sesquiterpenes including drimane-type sesquiterpenes, drimane-type sesquiterpene lactones, sesquiterpene lactams and coloratane sesquiterpenes. These original sesquiterpenes are associated with pharmaceutical activities.

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R É S U M É

Cinnamosma fragrans est une plante endémique utilisée en médecine traditionnelle. La répartition géographique de cette Canellacée est limitée à Madagascar. Les rares investigations phytochimiques réalisées sur cette plante ont permis de décrire des sesquiterpènes atypiques, dont des sesquiterpènes de type drimane, des lactones sesquiterpéniques de type drimane, des lactames sesquiterpéniques et des sesquiterpéniques de type coloratane. Ces sesquiterpènes originaux sont associés à des activités pharmacologiques.

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1. Introduction

Cinnamosma fragrans is an endemic medicinal plant used for decades in the Malagasy territory. This species of the family Canellaceae is better known under the

vernacular names of Mandravasarotra, Saro, or Sakarivohazo. This plant native to the northern and eastern part of the island is traditionally used in the treatment of several types of pathologies. *C. fragrans* is used to treat respiratory problems and limits the presence of parasites and gastrointestinal infections [1]. Decoctions of the bark are also used against muscular aches, fatigue or malarial symptoms [2]. The traditional use of this plant attracts interest.

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Few phytochemical investigations performed on this plant have revealed the presence of original sesquiterpenes including drimane-type sesquiterpenes, drimane-type sesquiterpene lactones, sesquiterpene lactams and coloratane sesquiterpenes. To date, 18 sesquiterpenes have been described in the bark or leaves of *C. fragrans*. These compounds are currently not well known and described.

C. fragrans is also known for its commercial essential oil. The essential oil has strong antimicrobial activities and is described in many applications for the treatment of infectious diseases in otorhinolaryngology. Consequently, some products based on this essential oil are also marketed for cosmetic use. For a review of the biological activities associated with the phytochemical composition of the Saro essential oil, see the article by Randrianarivelo et al [1].

After a botanical description of the plant, the objective of this review is to describe all sesquiterpenes present in *C. fragrans*. The biological activities associated with these secondary metabolites are also briefly described.

2. History, geographical distribution and botanical description of *C. fragrans*

The genus *Cinnamosma* was established by Henri Baillon in 1867 from a Madagascar tree, even though thirty years before him, Richard (director of the botanical garden of Bourbon at this period) had collected samples of the same plant in north of Madagascar at Diego Suarez. Henri Baillon also established a species and gave it the name *C. fragrans* due to its intense fragrance. Baillon read a description of this plant on 8 June 1867 in front of the Linnean Society of Paris and the identity of this plant was recognized [3].

C. fragrans belongs to the family of Canellaceae which is constituted by five genera (*Capsicodendron*, *Canella*, *Cinnamosma*, *Pleodendron*, and *Warburgia*) [2]. It is a family rather limited today, but once it counted many more species and had a more uniform geographical distribution in the world. *C. fragrans* like all species of the genus is endemic to Madagascar. It is distributed mainly in the northern and eastern part of the island [1]. It grows in dense and dry forests or in tropophytic forests on sedimentary, crystalline, calcareous or siliceous soils at low altitudes (between 0 and 800 meters). It is often near running waters, among shady stony ground or at the bottom of the gorge [4].

C. fragrans is a shrub or a small aromatic tree that has a pleasant smell and is always green. The bark, leaves and fruits have a burning and spicy taste. Its branches are cylindrical, slightly angular on younger stems and irregularly wrinkled longitudinally. The branches are sometimes marked by large lenticels. Its bark is light colored, yellowish-white and sometimes gray [3–5].

The flower of *C. fragrans* is sessile or subsessile, axillary and almost always solitary. It is small (circa 5 mm), actinomorphic, hermaphrodite and hypogynous. At the top of the peduncle, the flower has 3 to 7 bracts. These latter are large, of unequal size and deciduous. The lower bracts are

smaller and scaly to become increasingly large up towards the apex of the flower [3–5].

3. Sesquiterpenes of *C. fragrans*

Sesquiterpenes are secondary metabolites formed from three isoprene units where a further molecule IPP reacts with GPP to form farnesyl pyrophosphate (FPP). FPP is further converted to linear or cyclic products to obtain a sesquiterpene with a 15 carbon skeleton. Sesquiterpenes have a broad structural diversity but the majority and the most functional forms are cyclic. In *C. fragrans*, all sesquiterpenes described so far are cyclic (bicyclicofarnesane) [6–8].

3.1. Drimane-type sesquiterpenes

The name drimane designates a structure derived from drimenol. Drimenol is the first drimane sesquiterpene discovered. It was isolated from the bark of *Drimys winteri* Forst a species belonging to the Canellaceae. This family is a rich source of drimanes and these particular sesquiterpenes are scarcely isolated from other trees. Drimane-type sesquiterpenes have a structure with the absolute configuration depicted in Fig. 1 [9,10]. In *C. fragrans*, the first drimane-type sesquiterpene was identified in 1967 from an acetone extract of the bark. This sesquiterpene, called cinnamodial ($C_{17}H_{24}O_5$) (compound 1 in Fig. 2), is one of the compounds responsible for its pungent taste. This majority sesquiterpene is found not only in other species of *Cinnamosma* but also in other genera and species of the family Canellaceae [2,11,12]. The phytochemical investigations performed later have identified another majority compound in methanol extract: capsicodendrin (compound 2 in Fig. 2) [2]. The capsicodendrin with a molecular formula of $C_{34}H_{48}O_{10}$ was first discovered in another species of the family Canellaceae: *Capsicodendron dinisii* [12]. It is a pseudo-disesquiterpene since it corresponds to two sesquiterpene units connected by an ether bond [13]. Two other drimane-type sesquiterpenes were identified in this extract: cinnafragrin A ($C_{34}H_{48}O_{10}$) (compound 3 in Fig. 2) and cinnafragrin B ($C_{35}H_{50}O_{10}$) (compound 4 in Fig. 2). Both these compounds are also pseudo-disesquiterpenes. Cinnafragrin A is an epimer of capsicodendrin and cinnafragrin B is a methylated derivative of capsicodendrin [2]. Recently, another drimane-type sesquiterpene with a molecular formula of $C_{19}H_{28}O_7$ was discovered (compound 5 in Fig. 2) [14].

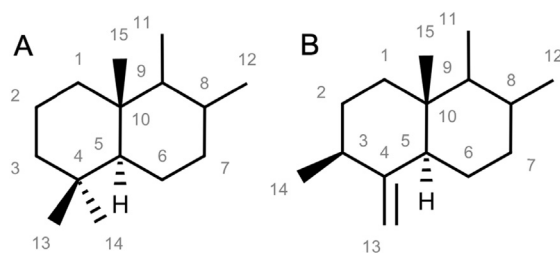


Fig. 1. Drimane (1) and coloratane (2) skeleton.

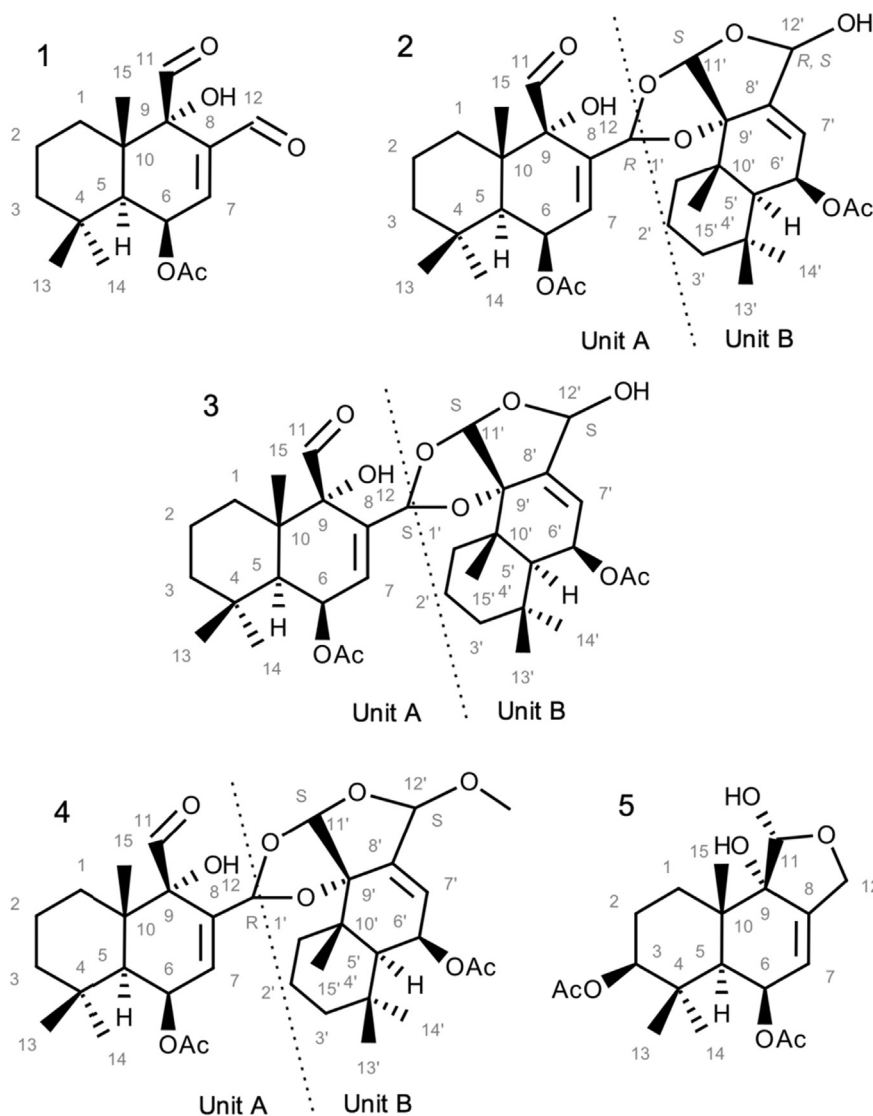


Fig. 2. Drimane-type sesquiterpenes.

3.2. Drimane-type sesquiterpene lactones

Sesquiterpene lactones are derivatives of sesquiterpene in which one of the methyl groups of the isopropyl group is oxidized to the lactone group [15]. These secondary metabolites are widely represented in the plant kingdom. They attract interest for their high biological activity due to their potential in the treatment of cancer and cardiovascular disease [7]. In *C. fragrans*, phytochemical explorations until today have been able to detect 7 drimane-type sesquiterpene lactones. Cinnamolide ($C_{15}H_{22}O_2$) (compound 6 in Fig. 3) and cinnamosmolide ($C_{17}H_{24}O_5$) (compound 7 in Fig. 3) were identified at the same time as cinnamodial from an acetone extract of the bark [16,17]. In parallel, the same research team has identified the same year three other minority compounds: bemarivolidide ($C_{17}H_{24}O_4$) (compound 8 in Fig. 3),

bemadienolidide ($C_{15}H_{20}O_2$) (compound 9 in Fig. 3) and fragrolide ($C_{15}H_{20}O_3$) (compound 10 in Fig. 3) [18]. Cinnafra-grin C ($C_{51}H_{70}O_{14}$) (compound 11 in Fig. 3) a trimeric drimane-type sesquiterpene lactone has been identified [2]. The unit C of this trimeric compound corresponds to ugandensolide, a sesquiterpene found in *Warburgia ugandensis* [19]. Recently, another drimane-type sesquiterpene lactone with a molecular formula of $C_{20}H_{28}O_8$ was discovered (compound 12 in Fig. 3) [14].

3.3. Sesquiterpene lactams

Sesquiterpene lactams have rarely been found in nature. In *C. fragrans*, 4 of them were discovered recently by ethyl acetate soluble extraction of a methanol extract of leaves [14]. Their molecular formulae are $C_{26}H_{35}O_5N$ (compound 13 in Fig. 4), $C_{26}H_{35}O_6N$ (compound 14 in Fig. 4), $C_{27}H_{35}O_7N$

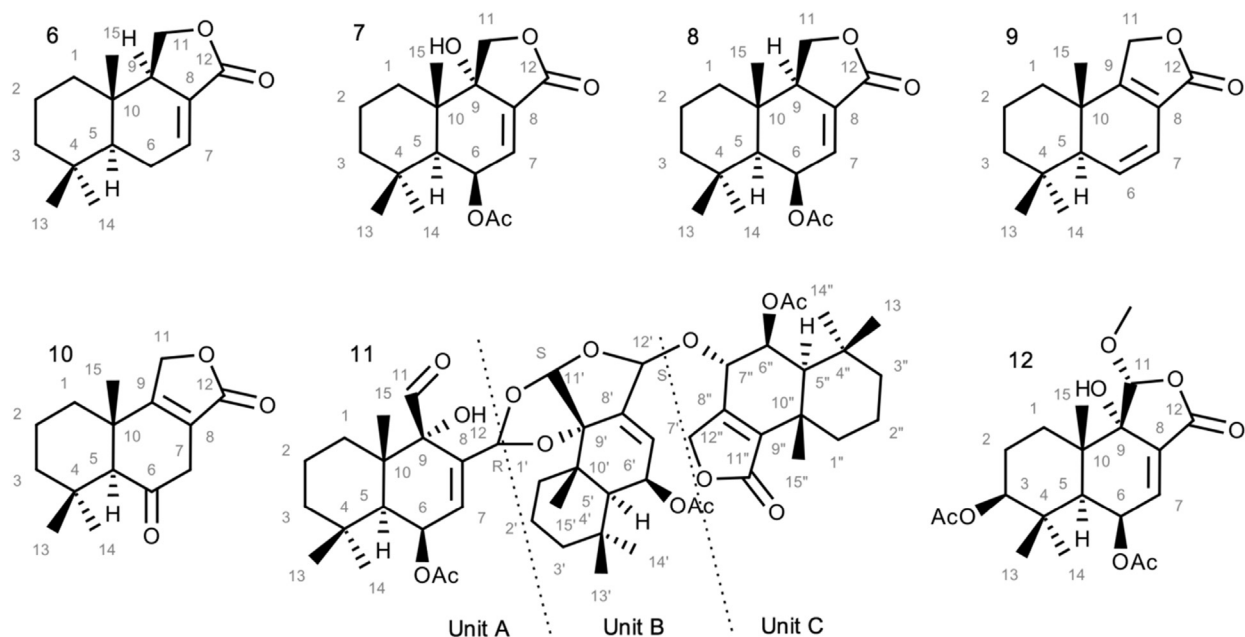


Fig. 3. Drimane-type sesquiterpene lactones.

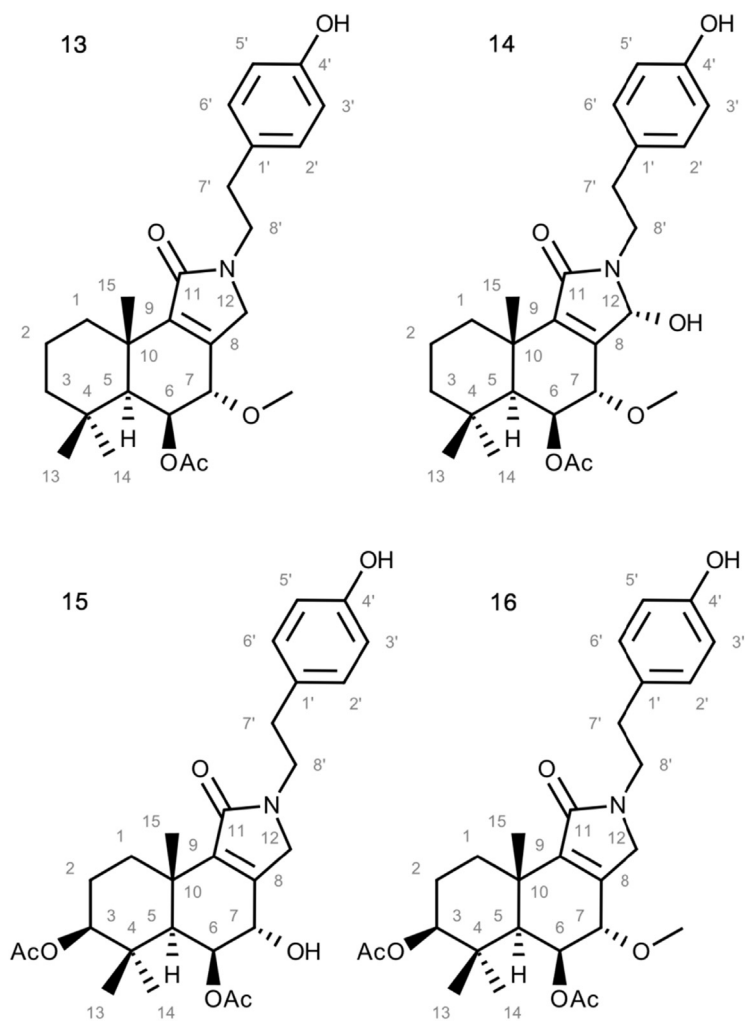


Fig. 4. Sesquiterpene lactams.

(compound 15 in Fig. 4), $C_{28}H_{37}O_7N$ (compound 16 in Fig. 4). Compound 14 is a hydroxy derivative of compound 13 in the C-12 position and compound 16 is a methylated derivative of compound 15 in the C-7 position. Compound 16 differs from compound 13 by the presence of a OAC group in the C-3 position. The authors suggest some acetylated compounds may be formed during extraction isolation procedures. The classification of these compounds is still a subject of debate. The presence of a nitrogen atom in a heterocyclic ring in these compounds can be used to classify these compounds in alkaloids also [14].

3.4. Coloratane sesquiterpenes

The coloratane structure corresponds to drimane where one of the methyl groups at position 4 is shifted to position 3 while leaving an exocyclic methylene group as depicted in Fig. 1 [20,21]. In *C. fragrans*, 2 coloratane sesquiterpenes were discovered in water soluble extraction of a methanol extract of leaves [22]. The molecular formulas of these two glycosyl compounds are $C_{21}H_{32}O_{10}$ (compound 17 in Fig. 5) and $C_{22}H_{34}O_{10}$ (compound 18 in Fig. 5). Compound 18 differs from compound 17 by the presence of a methyl group in the hydroxy group linked to C-11 position. The presence of this methyl group could be attributed to an artifact obtained during extraction and isolation procedures.

4. Biological activity associated to sesquiterpenes of *C. fragrans*

In 2006, Harinantenaina and Asakawa studied the ability of some sesquiterpenes of *C. fragrans* to inhibit the activity of alpha-glucosidase. This enzyme hydrolyses disaccharides into monosaccharides to be absorbed through

the intestinal mucosa. Such inhibitors are used in the treatment of type-2 diabetes. The results showed that capsicodendrin (compound 2) and cinnamodial (compound 1) induce a strong inhibition of the alpha-glucosidase activity. Cinnafrafrin A (compound 3) (epimer of capsicodendrin) showed no inhibitory activity and for cinnafrafrin B (compound 4), the methylated derivative of capsicodendrin, its inhibitory activity is low. The results highlight the importance of the structural configuration in the inhibitory activity [12].

In 2014, Nomoto and his collaborators studied the cytotoxicity activity toward lung adenocarcinoma A549 cells. In parallel, they studied anti-*Leishmania major* activity. Their results show that cinnamolide (compound 6), the drimane-type sesquiterpene lactone with a molecular formula of $C_{20}H_{28}O_8$ (compound 12) and the sesquiterpene lactam with the molecular formula $C_{26}H_{35}O_5N$ (compound 13) have a moderate cytotoxic activity and a moderate anti-*Leishmania major* activity [14]. The presence of these cytotoxic compounds does not appear to be an obstacle for the cosmetic application of *C. fragrans* as so far they have not been found in the essential oil of Saro [23].

5. Conclusion

C. fragrans has original sesquiterpenes. So far, phytochemical analyzes have identified 18 sesquiterpenes which can be grouped into four broad categories: drimane-type sesquiterpenes, drimane-type sesquiterpene lactones, sesquiterpene lactams and coloratane sesquiterpenes. These sesquiterpenes have interesting biological activities.

C. fragrans is a traditional use plant still under-exploited. Phytochemical investigations must continue to explore in depth the sesquiterpene contents of this plant and biological activity tests must be multiplied to better understand the medicinal properties associated with this endemic Malagasy plant.

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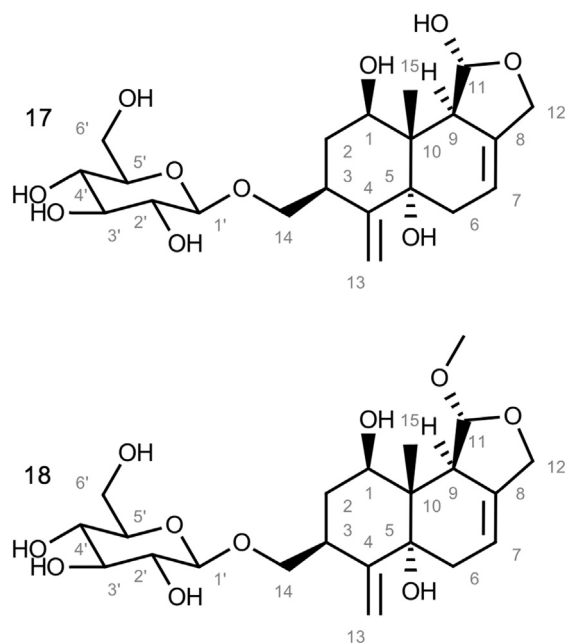


Fig. 5. Coloratane sesquiterpenes.

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